

**Remarks/Arguments:**

Claims 2 and 4-6 are amended to correct a typographical error and promote clarity of the claims. New claims 58-60 are added. Support for new claims 58-60 can be found, e.g., at page 17, lines 7-19 of the specification. Note that nt 244-265 of the integrin  $\beta 1$  gene (GenBank Accession No. NM 002211.2) is located within an exon of the integrin  $\beta 1$  gene (see Exhibit A). No new matter is introduced.

Claims 1-8, 11, 19, and 58-60 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

**CLAIM REJECTIONS UNDER 35 USC § 102(e)**

Claims 1, 3, 7, 11, and 19 are rejected as being anticipated by US 2003/0084471 to Beach et al. ("Beach"). Applicants respectfully traverse.

Claims 1 and 7 are directed to an isolated RNA comprising an artificial intron RNA that is released in a cell such as a eukaryotic cell, thereby silencing the function of a target gene. On the other hand, Beach discloses methods and compositions for RNA interference through double-stranded RNA (dsRNA). Although Beach mentions that an intronic sequence can be cloned into an expression vector for producing dsRNA, it suggests nothing whatsoever about creating an artificial intron RNA that can be released in a cell, thereby silencing the function of a target gene. To the contrary, Beach teaches only naturally-occurring introns. For example, Beaches states at page 2, right column, paragraph [0020]:

[0020] Another aspect of the present invention provides a method for attenuating expression of a target gene in cultured cells, comprising introducing an expression vector having a "non-coding sequence" which, when transcribed, produces double stranded RNA (dsRNA) in the cell in an amount sufficient to attenuate expression of the target gene. The non-coding sequence may include intronic or promoter sequence of the target gene of interest, and the dsRNA comprises a

nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence of the promoter or intron of the target gene ... (Emphasis added)

Beaches also states at page 9, right column, paragraph [0115]:

[0115] As used herein, the term "gene" or "recombinant gene" refers to a nucleic acid comprising an open reading frame encoding a polypeptide of the present invention, including both exon and (optionally) intron sequences. The nucleic acid may also optionally include non-coding sequences such as promoter or enhancer sequences. A "recombinant gene" refers to nucleic acid encoding such regulatory polypeptides, that may optionally include intron sequences that are derived from chromosomal DNA. The term "intron" refers to a DNA sequence present in a given gene that is not translated into protein and is generally found between exons. (Emphasis added)

Since Beach fails to teach an artificial RNA required by claims 1 and 7, it cannot anticipate claim 1 or 7. Claims 3, 11, and 19, dependent from claim 1, are also novel over Beach for at least the same reasons. Withdrawal of the rejections is thus respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 103(a)

Claims 1-8, 11, and 19 are rejected as being unpatentable over Beach in view of US 6,013,487 to Mitchell ("Mitchell"), Krawczak et al. (1992) Hum Genet 90:41-54 ("Krawczak"), Zhuang et al. (1989) PNAS 86:2752-2756 ("Zhuang"), and Coolidge et al. (1997) Nucleic Acids Research 25:888-896 ("Coolidge"). Applicants respectfully traverse.

Claims 1 and 7-8 are directed to an isolated RNA comprising an artificial intron RNA that is released in a cell such as a eukaryotic cell, thereby silencing the function of a target gene. As discussed above, Beach fails to teach such an RNA. Likewise, none of the secondary references cited by the Examiner discloses such an

RNA, and the Examiner did not rely on these references for disclosing such an RNA. Instead, the Examiner relied on the cited references for teaching a splice acceptor site (Mitchell), splice donor site (Krawczak), branch site (Zhuang), and polypyrimidine tract (Coolidge), respectively. As such, none of the secondary references can cure the defects of Beach.

Further, contrary to the Examiner's statement, one skilled in the art would not have been motivated to combine Beach and the secondary references to come up with the claimed invention. As discussed above, Beach discloses methods and compositions for RNA interference through dsRNA. Formation of such dsRNA does not depend on RNA splicing at all. See, e.g., EXAMPLE 3 at page 20, right column, paragraph [0219] – page 21, left column, paragraph [0223]; EXAMPLE 5 at page 22, right column, paragraphs [0242] – [0245]; EXAMPLE 7 at page 23, paragraphs [0251] – [0253] in Beach. Therefore, one skilled in the art would not have been motivated to modify the naturally-occurring intron sequences taught by Beach by replacing the splice acceptor sites, splice donor sites, branch sites, and polypyrimidine tracts in these introns with those taught by Mitchell, Krawczak, Zhuang, and Coolidge.

In light of the forgoing, Applicants respectfully submit that the prior art references cited by the Examiner, alone or in combination, do not render claims 1 and 7-8 obvious. Claims 2-6, 11, and 19, dependent directly or indirectly from claim 1, are also patentable over the cited art for at least the same reasons. Therefore, the rejections should be withdrawn.

### CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

Appl. No. 10/663,875  
Amdt. Dated May 26, 2009  
Reply to Office Action of January 23, 2009

Attorney Docket No. 89188.0050  
Customer No.: 26021

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (310) 785-4600 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,  
HOGAN & HARTSON L.L.P.

Date: May 26, 2009

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Attorney for Applicants

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Fax: 310-785-4601

# **Exhibit A**



All Databases



PubMed



Nucleotide



Protein



Genome



Structure



PMC



Taxonomy



Books



Nucleotide

My NCBI [2]  
[Sign In] [Register]

Search Nucleotide

for

Go

Clear

Limits Preview/Index History Clipboard Details

Format: GenBank FASTA Graphics More Formats ▼

Download ▼

Save ▼

NCBI Reference Sequence: NM\_002211.2

Change Region Shown

gi|19743812|ref|NM\_002211.2|

Customize View

This record has been replaced by NM\_002211.3

Comment Features Sequence

Sequence Analysis Tools

LOCUS NM\_002211 3700 bp mRNA  
 linear PRI 16-MAR-2008  
 DEFINITION Homo sapiens integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) (ITGB1), transcript variant 1A, mRNA.

## BLAST Sequence

Find regions of similarity between this sequence and other sequences using BLAST.

ACCESSION NM\_002211  
 VERSION NM\_002211.2 GI:19743812  
 KEYWORDS .

## Pick Primers

Design and test primers for this sequence using Primer-BLAST.

SOURCE Homo sapiens (human)  
 ORGANISM Homo sapiens  
 Eukaryota; Metazoa; Chordata; Craniata;  
 Vertebrata; Euteleostomi;  
 Mammalia; Eutheria; Euarchontoglires; Primates;  
 Haplorrhini;

## Recent Activity

Turn Off Clear

REFERENCE 1 (bases 1 to 3700)  
 AUTHORS Bhooopathi, P., Chetty, C., Kunigal, S.,  
 Vanamala, S.K., Rao, J.S. and  
 Lakka, S.S.

gi|19743812|ref|NM\_00

TITLE Blockade of tumor growth due to matrix metalloproteinase-9 inhibition is mediated by sequential activation of beta1-integrin,

ERK, and NF-kappaB  
 JOURNAL J. Biol. Chem. 283 (3), 1545-1552 (2008)  
 PUBMED 17331734  
 REMARK GeneRIF: These results indicate that MMP-9 inhibition induces apoptosis due to altered beta1-integrin expression in medulloblastoma and ERK activation plays an active role and functions upstream of NF-kappaB activation to initiate the

apoptotic signal.  
 REFERENCE 2 (bases 1 to 3700)  
 AUTHORS Saidi, S., Mahjoub, T., Slamia, L.B., Ammou, S.B., Al-Subaie, A.M. and

Almawi,W.Y.  
 TITLE Association of human platelet alloantigen 1  
 through 5 polymorphisms  
 JOURNAL Cerebrovasc. Dis. 25 (1-2), 81-86 (2008)  
 PUBMED [18057877](#)  
 REMARK GeneRIF: Observational study of gene-disease  
 association. (HuGENet)  
 REFERENCE 3 (bases 1 to 3700)  
 AUTHORS Bolduc,G.R. and Madoff,L.C.  
 TITLE The group B streptococcal alpha C protein binds  
 alphaIb beta1-integrin through a novel KTD motif  
 that promotes  
 internalization of GBS within human epithelial  
 cells  
 JOURNAL Microbiology (Reading, Engl.) 153 (PT 12), 4039-  
 4049 (2007)  
 PUBMED [18048918](#)  
 REMARK GeneRIF: Group B streptococci ACP binds alpha(1)  
 beta(1)-integrin  
 via the D1 domain that promotes GBS  
 internalization within  
 epithelial cells.  
 REFERENCE 4 (bases 1 to 3700)  
 AUTHORS Hu,K., Wu,C., Mars,W.M. and Liu,Y.  
 TITLE Tissue-type plasminogen activator promotes  
 murine myofibroblast  
 activation through LDL receptor-related protein  
 1-mediated integrin  
 signaling  
 JOURNAL J. Clin. Invest. 117 (12), 3821-3832 (2007)  
 PUBMED [18037995](#)  
 REMARK GeneRIF: tPA induces LRP-1 tyrosine  
 phosphorylation, which in turn  
 facilitates the LRP-1-mediated recruitment of  
 beta1 integrin and  
 downstream ILK signaling, thereby leading to  
 myofibroblast  
 activation.  
 REFERENCE 5 (bases 1 to 3700)  
 AUTHORS Yao,K., Tan,J., Ye,P., Wang,K., Xu,W., ShenTu,X.  
 and Tang,X.  
 TITLE Integrin beta1-mediated signaling is involved in  
 transforming  
 growth factor-beta2-promoted migration in human  
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 JOURNAL Mol. Vis. 13, 1769-1776 (2007)  
 PUBMED [17960115](#)  
 REMARK GeneRIF: TGF-beta2 promoted human lens  
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 migration in vitro. Integrin beta1 and integrin-  
 mediated signaling  
 are necessary for TGF-beta2-promoted adhesion  
 and migration in  
 human lens epithelial cells.  
 Publication Status: Online-Only  
 REFERENCE 6 (bases 1 to 3700)  
 AUTHORS Languino,L.R. and Ruoslahti,E.  
 TITLE An alternative form of the integrin beta 1  
 subunit with a variant  
 cytoplasmic domain

JOURNAL J. Biol. Chem. 267 (10), 7116-7120 (1992)  
 PUBMED [1551917](#)  
 REFERENCE 7 (bases 1 to 3700)  
 AUTHORS Otey, C.A., Pavalko, F.M. and Burridge, K.  
 TITLE An interaction between alpha-actinin and the beta 1 integrin subunit in vitro  
 JOURNAL J. Cell Biol. 111 (2), 721-729 (1990)  
 PUBMED [2216421](#)  
 REFERENCE 8 (bases 1 to 3700)  
 AUTHORS Sonnenberg, A., Linders, C.J., Modderman, P.W., Damsky, C.H., Aumailley, M. and Timpl, R.  
 TITLE Integrin recognition of different cell-binding fragments of laminin (P1, E3, E8) and evidence that alpha 6 beta 1 but not alpha 6 beta 4 functions as a major receptor for fragment E8  
 JOURNAL J. Cell Biol. 110 (6), 2145-2155 (1990)  
 PUBMED [1693624](#)  
 REFERENCE 9 (bases 1 to 3700)  
 AUTHORS Vogel, B.E., Tarone, G., Giancotti, F.G., Gailit, J. and Ruoslahti, E.  
 TITLE A novel fibronectin receptor with an unexpected subunit composition (alpha v beta 1)  
 JOURNAL J. Biol. Chem. 265 (11), 5934-5937 (1990)  
 PUBMED [2138612](#)  
 REFERENCE 10 (bases 1 to 3700)  
 AUTHORS Bodary, S.C. and McLean, J.W.  
 TITLE The integrin beta 1 subunit associates with the vitronectin receptor alpha v subunit to form a novel vitronectin receptor in a human embryonic kidney cell line  
 JOURNAL J. Biol. Chem. 265 (11), 5938-5941 (1990)  
 PUBMED [1690718](#)  
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 [WARNING] On Apr 11, 2008 this sequence was replaced by gi:[162512239](#).  
 On Mar 26, 2002 this sequence version replaced gi:[4504766](#).

Summary: Integrins are heterodimeric proteins made up of alpha and beta subunits. At least 18 alpha and 8 beta subunits have been described in mammals. Integrin family members are membrane receptors involved in cell adhesion and recognition in a variety of processes including embryogenesis, hemostasis, tissue repair, immune response and metastatic diffusion of tumor cells. The protein encoded by this gene is a beta subunit. Six alternatively spliced variants have been found for this gene which encode five proteins with alternate carboxy termini.

Transcript Variant: This variant (1A) is the most common variant and has an alternate 5'UTR due to the use of the alternate proximal promoter. Variants 1A and 1E encode the same isoform.

Publication Note: This RefSeq record includes a subset of the publications that are available for this gene. Please see the Entrez Gene record to access additional publications.  
 COMPLETENESS: full length.

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gene



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3661 gaagttattt attaaatag cctaaaatac ttaaatcgga

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